Specification Objections

1. The Examiner has objected to the specification for not describing the identity or function of the protein set forth by SEQ ID NO: 4, and its relationship to the proteins set forth by SEQ ID NOs: 2 and 3.

Identity of SEQ ID NO: 4: SEQ ID NO: 4 corresponds to the mature form of human brain carboxypeptidase B (HBCPB), SEQ ID NO: 3 corresponds to the pro-form of HBCPB, and SEQ ID NO: 2 corresponds to the pre-pro-form of HBCPB. This is explained, for instance, on p. 7. lines 10-19 as well as p. 5, 3rd full paragraph, of the response to the restriction requirement. The distinctions between these differing forms of the protein are further illustrated on p. 23, lines 22-24, which describes Figure 4. Figure 4 shows that the pre-pro-form of HBCPB contains 360 amino acids, the pro-form of HBCPB contains 338 amino acids, and the mature form of HBCPB contains 246 amino acids. SEQ ID NO: 4, which is a 246 amino acid sequence, corresponds to the mature, approximately 30 kDa form of HBCPB. Thus, SEQ ID NOS: 2, 3 and 4 represent different maturation stages of the same enzyme.

Function of SEQ ID NO: 4: The specification shows that the 40 kDa and 30 kDa forms of HBCPB, which correspond to the proteins set forth in SEQ ID NOs: 2 and 4, respectively, have similar proteolytic activities. These proteolytic activities are shown in experiments described starting on p. 26, line 18, and ending on p. 27, line 35. Specifically, hippocampus brain homogenate proteins, after elution from a Sepharose column, were subjected to native PAGE electrophoresis. Fractions separated by size were assayed for proteolytic activity against natural brain APP. As described on p. 27, lines 28-35, an approximately 40 kDa fraction (fraction 19) and an approximately 30 kDa fraction (fraction 11) both demonstrated similar specific proteolytic activities. The 30 kDa protein was then subjected to amino acid sequencing described on page 29, lines 12-20 and depicted in Table 1. The sequence of the amino terminus of the 30 kDa protein, which is depicted in Table 1 and as the underlined sequence in Figure 3, identified the 30

kDa protein as the protein set forth by SEQ ID NO: 4. Therefore SEQ ID NO:4 has the same kind of proteolytic activity as SEQ. ID NO:3.

These experiments are consistent with the respective structures of SEQ ID NOS: 2, 3 and 4. Amino acids that are known to be involved in the catalytic mechanism (i.e., zinc binding and substrate binding) are circled and boxed, respectively, in Figure 3. The description of Figure 3 is on p. 23, lines 17-20. All of these circled and boxed residues are located in the C-terminal half of the protein starting with a histidine at residue number 181 and ending with an aspartic acid at residue 333. The proteins set forth in SEQ ID NOs: 2, 3 and 4 all contain these residues because the shortest of the proteins, which is set forth in SEQ ID NO: 4, starts at residue 115 of the full length protein. The 22 and 92 amino acid signal sequence and activation domains are not expected to contribute to the catalytic activity of HBCPB. Based on these common structural features, all three maturation stages (i.e., SEQ ID NOs: 2, 3 and 4) contain the domains needed for carboxypeptidase activity. Such is consistent with the experimental results described in the previous paragraph.

2. The Examiner has objected to the specification for not stating the identity of the human brain carboxypeptidase used in Example 7. The human brain carboxypeptidase used in Example 7 is a purified brain-derived 40 kDa HBCPB that corresponds to SEQ ID NO: 3.

Claim Objections

The objections to claims 10 and 32 have been noted and correcting amendments are included in this response.

Claim Rejections: 35 USC § 112, Second Paragraph

The Examiner has rejected claims 2, 3, 5, 6, 7, 9, 11, 18-20, 24-26, and 32 under 35 USC § 112, second paragraph as being indefinite in the recitation of "hybridizes with." Claim 2 has been amended to remove the phrase in which these words appear.

Claim Rejections: 35 USC § 112, First Paragraph: Enablement

The Examiner has rejected claims 2-7, 11, 18-20, 24-26, 32, 34, and 35 under 35 USC § 112, first paragraph, as not providing enablement for a protein set forth by SEQ ID NO: 4 or a nucleic acid that encodes a protein set forth by SEQ ID NO: 4.

The Examiner acknowledges that the specification is enabling for polynucleotides encoding proteins having peptidase activity toward brain APP wherein the polynucleotide is set forth by SEQ ID NO: 1 and the proteins are set forth by SEQ ID NOs: 2 or 3, or by proteins having ≥90% identity with SEQ ID NOs: 2 or 3. The Examiner says , however, that the same is not true for a polynucleotide encoding a protein that has peptidase activity toward brain APP wherein the protein is set forth by SEQ ID NO: 4 or has ≥90% identity with SEQ ID NO: 4.

Applicants understand the concern underlying the Examiner's remarks is the same as that addressed in the previous paragraph. As previously discussed, SEQ ID NO:4 has the same proteolytic activity as SEQ ID NOs: 2 and 3. Therefore SEQ ID NO:4 and sequences showing 90% sequence identity thereto are enabled for the same reasons as SEQ ID NOs 2 and 3 and sequences showing 90% sequence identity thereto.

Claim Rejections: 35 USC § 112, First Paragraph: Written Description

Claims 2-7, 11, 18-20, 24-26 are rejected under 35 USC § 112, first paragraph, for lack of written description, the Examiner says that the specification only teaches the structure and function of two representative species of polynucleotides and proteins, and further that the function of the protein set forth by SEQ ID NO: 4 is not described. Applicants understand the Examiner's underlying concern to be the same as that described in previous paragraphs, namely that the function of SEQ ID NO:4 is not described. However, as explained above SEQ ID NO:4 has the same function as SEQ ID NO:2 and 3. Thus, it is submitted that applicants have described representative species for the genera claimed.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 2 was amended as follows:

2. (Twice Amended) A protein comprising peptidase activity towards brain APP, wherein said protein ~~is selected from the group consisting of,~~

~~(a) a protein comprising~~ comprises an amino acid sequence in which one or more amino acids are replaced, deleted, inserted, and/or added to the amino acid sequence of any one of SEQ ID NOs: 2 to 4, wherein said protein has 90% or greater identity to SEQ ID NOs 2, 3, or 4~~;~~

~~(b) a protein encoded by a DNA that hybridizes with a DNA comprising the nucleotide sequence of SEQ ID NO: 1, wherein said protein has 90% or greater identity to SEQ ID NOs 2, 3, or 4;~~

~~(c) a protein comprising the amino acid sequence of any one of SEQ ID NOs: 2 to 4~~.

Claim 10 was amended as follows:

10. (Twice Amended) A polynucleotide encoding the C-terminal 14 amino acids of SEQ ID NO: 2 having the amino acid sequence of Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys, or its complementary strand.

Claim 32 was amended as follows:

32. (Amended) The protein of claim 2, wherein said protein comprises the C-terminal 14 amino acids of Ser Asn Pro Pro Val Glu Lys Leu Leu Pro Leu Ser Leu Lys.